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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/210,747	12/15/98	BRIGGS R	0029577957

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EXAMINER	
PORTNER, V	
ART UNIT	**PAPER NUMBER**
1645	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

File Copy

Office Action Summary	Application No. 09/210,747	Applicant(s) Briggs et al
	Examiner Portner	Group Art Unit 1645

☒ Responsive to communication(s) filed on *Aug 7, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *34, 35, and 38-50* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *34, 35, and 38-50* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 34-35,38-50 are pending.

Claims 36-37 have been canceled.

1. Finality of the last Office action is withdrawn.

Rejections Withdrawn

2. Upon processing the terminal disclaimer submitted April 7, 2000 and it being found ~~effective~~ proper the rejection of claims 34-35 and 38-44 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,849,305 for reasons of record, as well as claim 5 of US Pat. 5,824,525 and claims 13-16 of US Pat. 5,587,305 will be withdrawn.

Rejections Maintained

3. Claims 38-39 and 43-44 recite modes of administration of the composition but these limitations are not further limiting of the claim from which they depend because a mode of administration does not further define the components present in the composition

being claimed and the recitation of an intended use does not define a vaccine component.

4. Claims 34, 38,39,46,47 rejected under 35 U.S.C. 102(b) as being anticipated by Cruz et al (1990).

Cruz et al disclose strains of Pasteurella haemolytica which were modified through a series of internal deletion in the lktA (leukotoxin-A) gene and leukotoxin C gene. Inherently these strains would have the now claimed characteristics and therefore anticipates the now claimed invention.

5.Upon reconsideration of the disclosure relative to the claimed invention, the following new grounds of rejection are being made.

Claim Rejections - 35 U.S.C. § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 34-35,38-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point

out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-35,38-50 recite a vaccine that comprises a Pasteurella haemolytica bacterium that comprises a mutation in a gene,wherein the recited mutation need not attenuate the bacterium, as any type of mutation is claimed and the effect of the mutation need not have measurable effect as the bacterium is not defined to be attenuated, and leukotoxin mutation need not evidence any measurable change from the native toxoin, such as reduced toxicity. The bacterium is not defined as an attenuated bacterium and therefore does not distinctly claim Applicant's invention.

Claims 34-35,38-40 recite an improper Markush group, as the members recited are not so linked by structure and function as to define obvious species one over the other. Each gene codes for a different protein with different function for the bacterium. Correction is requested.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable

> any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 34-35,38-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of AroA mutants through the utilization of PhaI, does not reasonably provide enablement for Pasteurella haemolytica vaccines that comprise any mutations in the AroA, PhaI gene, leukotoxin C, leukotoxin A genes and the use of these strains as a vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

The claims recite a vaccine for induction of a protective immune response against Pasteurella haemolytica infection, wherein the recited mutation need not attenuate the bacterium, as any type of mutation is claimed and the effect of the mutation need not have any effect as the bacterium is not defined to be attenuated, and leukotoxin mutation need not evidence any measurable change from the native toxoin, such as reduced toxicity.

The specification teaches compositions that comprise Pasteurella haemolytica mutants with an intended use for

administration, and teaches that the composition may be administered by **any** conventional route in use in the field of vaccines(see claims 38 and 39).

The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity, in the case of the instantly claimed invention, the protection or prevention of infection would be against pathogenic *Pasteurella haemolytica*.

The specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity for prevention or treatment of Pasteurella haemolytica, especially using only an vaccine preparation without co-administration of said preparation together with an adjuvant.

Data obtained from challenge experiments must demonstrate an art recognized standard of improvement over the control in order for the composition to be considered as being useful for treatment or prevention of infection. This information is essential for the skilled artisan to be able to use the claimed composition (vaccines) for their intended purpose of preventing *Pasteurella haemolytic* infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would

not be able to accurately predict if protective immunity has been induced.

The prior art:

a. Corstvet, (US Pat. 5,256,415, (col. 1, lines 22-39) teaches that vaccines have been developed for P.haemolytica but with **limited success** and are known to produce marked swelling and abscessation at the site of vaccination in greater than 5% of the animals.

b.Weekley et al (1993) teach that vaccination against pasteurellosis has had limited efficacy in preventing development of BPP (Martin 1983) and suggest that vaccination may temporarily **impair disease resistance** during the post vaccination period (see page 447, col. 1, paragraph 2).

c.Confer et al (1985) teach that "although bacterins may induce a detectable serum antibody response, they **do not induce protection** against transthoracic challenge exposure to P.haemolytica."

d. Confer (1993) reviewed Pasteurella haemolytica vaccines and found:

(1)Confer 1989, (see Confer 1993, page 361, paragraphs 2-3) found that immunization of ruminants with P.haemolytica capsular polysaccharide, live or killed whole cell

preparations results in an antibody response to the capsule but found that the intensity of the antibody response to LPS did not correlate with resistance to experimental challenge.

(2)Conlon & Shewen (1991) reported that vaccination of calves with purified capsular polysaccharide was ineffective to protect calves against P.haemolytica challenge.

(3)Morton et al (1990) found that vaccination of cattle with OMP-enriched preparation induced serotype specific immunity against experimental challenge and raises the question of how a single serotype strain could protect against all other serotypes of Pasteurella haemolytica (see page 361, paragraph 4). Vaccination with live bacteria resulted in high titers of neutralizing antibodies (362, paragraph 2) but have been shown to have undesirable side effects such as fever, localized abscesses and lameness (Confer, 1986c, page 363, paragraph 1).

e. Conlon et al (1993) states that Pasteurella bacterins used extensively in the past induced anaphylaxis in some vaccinated animals (see page 771, col. 1, paragraph 2, last half of paragraph).

f. Zeman et al (1993, abstract) show that through the use of an avirulent live Pasteurella vaccine, some of the bacteria **caused meningitis, injection site abscessation and/or cellulitis**

and polyarthritis. Pasteurella haemolytic was isolated from the brain, joint or injection site of several animals. The vaccine bacterium produced systemic infection and therefore did not induce protection.

g. Weekley et al (1993) teach that through the use of a Pasteurella haemolytic whole cell vaccine, **an imbalance in the adrenergic responsiveness of vascular smooth muscle** was caused due to exposure to the vaccine derived strain.

h. Chandrasekaran et al (1991) evaluated a commercially available vaccine for Pasteurella,"Carovax" and found that it did not produce any significant reduction of lung lesions caused by P.haemolytica and/or P.multocida. When the animals were challenged with both P.haemolytica and P.multocida, the vaccine that contained isolated strains of Pasteurella haemolytica type 7 and Pasteurella multocida types A and D was unsatisfactory.

i. Chengappa et al (1989) evaluated a live vaccine that comprised both Pasteurella multocida A:3 and Pasteurella haemolytica A:1 and found that all calves had a slight increase in immunoglobulin M and G classes, but the differences were not statistically significant over the control.

j. Mosier et al (1989) reported that while early reports of vaccine induced protection was suggested, the initial vaccines

were of questionable protective value. The use of bacterins (killed cells), bacterin-virus combination vaccines and viral vaccines were found that they "did not consistently reduce disease in experimental trials or field use" (abstract).

k. Jericho et al (1982) found that live Pasteurella haemolytic in aerosol form did not protect against experimental disease (see entire abstract).

l. Purdy et al (1986,abstract) reported that a live Pasteurella haemolytica serotype I vaccine "had no significant effect on performance, morbidity, or mortality. There was no significant difference between the vaccinated and nonvaccinated calves in the number of times Pasteurella was isolated."

Clearly the prior art shows unpredictability of vaccine compositions for Pasteurella haemolytica, wherein the administration of a "vaccine" composition could also induce negative side effects and cause detrimental effects to include loss of live-stock.

The vaccine art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit in vivo protective immunity. Accordingly, the art indicates that it would require undue

experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

Given the lack of guidance on how to obtain the desired effect using a composition comprising any form of mutant Pasteurella haemolytica (live, bacterin, killed) to induce an immune response to protect against infection, and in light of the teachings of the prior art which show that vaccines comprising Pasteurella haemolytica are unpredictable in methods of treating or preventing infection the skilled artisan could not make and use the claimed invention. No evidence is of record showing that **any** composition could confer the desired and claimed effect. No working examples are shown which convey the missing information. Therefore, the skilled artisan could not use **any** composition of Pasteurella haemolytic bacterium that comprises a mutation to obtain the desired effect of preventing or treating infection without undue experimentation.

10. Claims 34-35,38-40, 48-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification broadly describes, as part of the invention, a Pasteurella haemolytic bacterium that comprises a mutation in the neuramidase gene of this bacterium. The specification does not describe the coding region of the gene that would be translated into the neuramidase polypeptide. The statement that the invention encompasses mutations in the neuraminadase gene is made at page 7, lines 11-12. The disclosure does not meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The specification only discloses the existence of leukotoxin B, D and neuraminidase genes, but no coding regions, no cosmid clones, no restriction endonuclease fragments that encode the Pasteurella haemolytic neuraminidase are described. No specific mutations are described that would result in a mutant Pasteurella haemolytica leukotoxin B or D bacterium. No recombinant host cells are disclosed that comprise a heterologous sequence that expresses the protein and would be readily obtainable by a repeatable process described and disclosed in the instant

specification that could be used to produce a neuraminidase mutant bacterium of Pasteurella haemolytica.

Production of a mutant strain of Pasteurella hemolytica through introduction of random mutations using known methods, and selecting for a phenotypic neuraminidase, leukotoxin B or leukotoxin D negative strain does not meet the claimed invention which is a strain that has a mutation in the gene. Lack of expression of a gene product could be due to mutations in the promoter region or, the membrane secretory system and would result in a phenotypically negative mutant strain. Use of random mutations to obtain a phenotype does not provide written descriptive support for the claimed genetic mutant strains that evidences mutations in the leukotoxin B, D and neuraminidase genes.

Applicants have not described nor disclosed the "operon" which encodes the "neuraminidase" gene. A functional bacterial gene encompasses much more than a protein coding region (see Davis et al., Microbiology, page 267). A bacterial gene is conventionally associated with positive and negative controlling elements such as promoters and regressors in a concordantly regulated transcription unit called an operon, without which, no protein is expressed. The specification fails to describe the functional gene *per se* (i.e., operon) and which applicants have intended to be encompassed by the comprising language of the instant claims as set forth *supra*. In a bacterial genome, the recitation of "comprising" includes regulatory sequences which

are essential to the operation and function of the structural gene in the operon. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Similarly, applicants have not disclosed any information with respect to the neuraminidase gene of Pasteurella haemolytica, therefore mutations in this gene clearly lack written description. No specific means or methods of obtaining a leukotoxin B or D mutant strain of Pasteurella haemolytica that would also serve to induce a protective immune response have been described. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.
vgp
November 8, 2000

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